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| 09/765,555      | 01/19/2001  | Carlos F. Barbas III | 278012001420        | 1190             |

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EXAMINER

IBRAHIM, MEDINA AHMED

ART UNIT PAPER NUMBER

1638

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/765,555

**Applicant(s)**

BARBAS ET AL.

**Examiner**

Medina A Ibrahim

**Art Unit**

1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 14 June 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☒ Claim(s) 11 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 October 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date. _____  | 6) <input type="checkbox"/> Other: _____                                    |

Continuation of Disposition of Claims: Claims pending in the application are 1,3-8,11,13-16,18-22,28-30,36-44,46,48-66,68-72,74,76-85,88,91-95,98-100 and 133-137.

Continuation of Disposition of Claims: Claims rejected are 1,3-8,13-16,18-22,28-30,36-44,46,48-66,68-72,74,76-85,88,91-95,98-100 and 133-137.

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### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's response filed 06/26/04 in reply to the Office action of 03/09/04 has been entered. Claims 1, 3-8, 11, 13-16, 18-22, 28-30, 36-44, 46, 48-66, 68-72, 74, 76-85, 88, 91-95, 98-100, 133-137 are pending and are examined. The indicated allowability of claims 1, 3-8, 13-16, 18-22, 29-22, 29-30, 36-44, 46, 48-49, 51-53, 55, 57-66, 68-72, 74, 76-85, 88, 91-95, and 98-100 are withdrawn upon further consideration.

This Office action contains NEW GROUNDS OF OBJECTIONS and REJECTIONS not necessitated by Applicant's amendments. Therefore, this action is non-final. The delay in applying these grounds of rejections and objection is regretted.

#### ***Claim Objections***

Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

#### ***Sequence Listing***

Applicant's CRF and paper sequence listing filed 16 October 2002 have been entered. However, this application fails to comply with the requirements of 37 CFR 1.821-1.825 because the peptide sequence on page 32, line 1, has not been identified by SEQ ID NO: Also, some of the sequence listing of Fig. 24, for example the sequences on paragraphs (7)-(10) have not been identified by SEQ ID NO: Applicant is

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respectfully requested to identify the sequence on page 32 and the sequences in Fig. 24 or to submit a new Sequence Listing, which comprises said sequences. In addition, the sequence listing filed 10/16/02 does not match the sequences listed on Figure 24. For example, SEQ ID NO: 1 has 532 bp in the sequence listing and 531 in the sequence of Fig. 24. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

Claims 1, 3-8, 13-16, 18-22, 29-30, 36-44, 46, 48-49, 51-53, 55, 57-66, 68-72, 74, 76-85, 88, 91-95, and 98-100 and 133-137 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression level of a target gene in a plant /plant cell by transforming the plant/ cell with a nucleotide sequence encoding a synthetic zinc finger proteins that binds to a specific target nucleotide sequence with in the target gene, an expression vector comprising said nucleotide sequence, transformed plant, plant cells, and seed comprising said expression vector, does not reasonably provide enablement for any method to modulate the expression of a target gene with any zinc finger protein capable of binding to any 18 nucleotides within the target gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is repeated in part for the reasons set forth in the Office actions of 03/09/04 and 05/21/03. Applicant's arguments filed 06/14/04 have been considered but are not deemed persuasive.

The claims are broadly drawn to a method for modulating the expression of a target gene in a plant/cell comprising introducing into the plant/cell a nucleotide sequence encoding a synthetic zinc finger protein that binds to a target nucleotide sequence of 18 nucleotides within the target gene or a complementary strand thereof, an expression vector comprising said nucleotide sequence, transformed plant, plant cells and seed comprising said expression vector. The claims also encompass target nucleotide sequence that can be exogenous or endogenous to the target gene and zinc finger proteins comprising multiple finger regions and linker region of from 2 to 10 amino acid residues in length. The claims also encompass finger proteins directed to a specific organelles of a plant via transit peptides. In contrast, the specification is enabling for the use of synthetic zinc finger proteins that are designed to target unique sequences of the formula (GNN)<sub>6</sub> or sequences containing 18 consecutive nucleotides wherein some of the GNN triplets have been substituted by TGA; expression vectors, transgenic plants, plant cells, and seeds produced by said method.

The specification is not enabling for a method that employs a synthetic zinc finger protein that are capable of modulating the expression a target gene by binding to any 18 nucleotides of the target gene. While prior art provides several methods on the development of synthetic zinc finger proteins, the approach is limited to the development of zinc finger proteins that specifically bind targeted 18 contiguous nucleotides sequences and methods for using said synthetic zinc finger proteins in mammalian and yeast system. Choo et al (Current Opinion in Structural Biology (2000), 10:411-418) teach about the advances in zinc finger engineering to target specific DNA

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sequences within a target gene. Choo et al specifically states "(A)lthough the general strategy of combining preselected monomers is clearly effective, the major caveat in its implementation is that the selection of individual zinc fingers (in the context of a multifinger protein) has so far yielded monomers that specifically recognize only DNA triplets of the form GNN (i.e. trinucleotides having guanine fixed in the 5' position). This in turn means that it is only possible to design proteins that specifically bind DNA sequences of the form GNNGNN.... (i.e. sequences having guanine at every third base position)". Therefore, given this limitation in designing zinc finger proteins that recognize wide variety of DNA sequences, claims drawn to a method that involves any 18 nucleotides of the targeted gene cannot be practiced without trial and error experimentation considered undue.

Since Applicant's representative has agreed on the proposed amendments faxed on 08/30/04 and discussed during the telephone interview on 08/31/04, the following claim amendments are suggested which will place the application in condition for allowance.

Claim 1. A method to stably modulate the expression level of a target gene in a plant cell comprising [the steps of]:

(a) introducing into a plant cell an expression vector comprising a nucleotide sequence encoding a synthetic zinc finger protein [, said zinc finger protein] that specifically binds [binding] to a target nucleotide sequence, or a complementary strand thereof, within a target gene, wherein said target nucleotide sequence is of the formula (GNN)<sub>6</sub>, wherein N is any one of the A, T, C, or G [ comprises 18 nucleotides] and

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wherein said zinc finger protein is a hexadactyl zinc finger protein comprising one individual zinc finger DNA binding site [protein] with mutations at one or more of the base-contacting positions; and

(b) culturing said plant cell under conditions such that said finger protein is stably expressed and binds [allowing said zinc finger protein to bind] to said target nucleotide sequence, whereby the expression of said target gene in said plant cell is stably modulated.

Claim 3 should be cancelled.

Claim 4. A method to stably modulate the expression level of a target gene in a plant comprising [the steps of]:

(a) introducing into a plant cell an expression vector comprising a nucleotide sequence encoding a synthetic zinc finger protein [, said zinc finger protein] that specifically binds to a target nucleotide sequence, or a complementary strand thereof, within a target gene, wherein said target nucleotide sequence is of the formula (GNN)<sub>6</sub>, wherein N is any one of the A, T, C, or G [ comprises 18 nucleotides] and wherein said zinc finger protein is a hexadactyl zinc finger protein comprising one individual zinc finger protein with mutations at one or more of the base-contacting positions; and

(b) culturing said plant cell under conditions such that [wherein] said finger protein is stably expressed [produced] and binds to said target nucleotide sequence; and



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(c ) growing a plant from the plant cell, whereby the expression of said target gene in said plant is stably modulated.

Claim 8 (Currently amended) The method of claim 6 [1], wherein the target nucleotide sequence is upstream of the target gene [a promoter of a regulatory protein].

Claim 11. The method of claim 1, wherein the target [targeted] nucleotide sequence comprises 18 consecutive nucleotides with TGA triplets [is of the formula (GNN)<sub>6</sub> and wherein N is any one of A, T, C, or G].

At claim 13, ---cell--- has been inserted after "plant".

Claim 28 (Currently amended): The method of claim 1, wherein the target gene encodes a protein [encoded by the target gene] that confers [enhances an input or output] a desired trait in said plant cell.

At claim 29, "or" after "nutrient" has been replaced with ---protein, ---.

Claim 30. The method of claim 29 [19], wherein the target gene encodes an enzyme [or a cofactor].

At claim 39, "host" before "plant" has been deleted.

At claim 42, "about" has been deleted in each occurrence.

At claim 48, ---plant cell--- has been inserted after "monocot".

Claim 49 has been cancelled.

At claim 52, "claim 1" has been replaced with ---claim 51---.

At claims 53-54, "claim 52" has been replaced with ---claim 51---.

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Claim 55. The method of claim 4 [1], wherein the modulation of the gene expression changes the phenotype of the plant [cell].

At claim 58, ---further--- has been inserted before "comprises".

Claim 60 has been cancelled.

At claims 64-65, "claim 1" has been replaced with ---claim 61---.

Claims 68-69 have been cancelled.

Claim 70. A method of stably modulating the level of a compound in a plant cell, which method comprises introducing into a plant cell an expression vector comprising a nucleotide sequence encoding a synthetic zinc finger protein [, said zinc finger protein] that specifically binds to a target nucleotide sequence, within a target gene encoding said compound, wherein said target nucleotide sequence is of the formula (GNN)<sub>6</sub>, wherein N is any one of the A, T, C, or G [comprises 18 nucleotides] and wherein said zinc finger protein is a hexadactyl zinc finger protein comprising one individual zinc finger protein with mutations at one or more of the base-contacting positions; and culturing said plant cell under conditions wherein said finger protein is stably expressed and binds to said target nucleotide sequence, whereby the level said compound in said plant cell is stably modulated.

Claim 74. An expression vector comprising a nucleotide sequence encoding a synthetic zinc finger protein selected from the group consisting of ZFPm1, ZFPm2,

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ZFPm3, ZFPm4 and ZFPAp3, said zinc finger protein specifically binds to a target nucleotide sequence, or a complementary strand thereof, within a target gene, wherein said target nucleotide sequence comprises 18 consecutive nucleotides and wherein said zinc finger protein is a hexadactyl zinc finger protein comprising one individual zinc finger protein with mutations at one or more of the base-contacting positions.

Cancel claim 75.

Claim 76. A stably transformed plant cell comprising the expression vector of claim 74, wherein said synthetic zinc finger protein is expressed under the control of a promoter..

Claim 79-82 has been cancelled.

Claim 83. The stably transformed plant cell of claim 76, wherein the [zinc finger protein gene is further controlled by a second] promoter is an inducible promoter.

Claim 84 has been cancelled.

At claim 85, "finger sequences" has been replaced with ---fingers---.

At claim 88, ---from a plant--- has been inserted before "selected". Also, "maize" in line 3, has been deleted.

At claim 93, "genetically modified" has been replaced with --stably transformed--.

At claim 95, ---from a plant--- has been inserted before "selected". Also, "maize" in line 3, has been deleted.

Claim 99. A method to stably modulate the expression level of a target gene in a plant cell, which method comprises culturing the plant cell of claim 76.

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Claim 100. The method of claim 99 [, wherein] further comprising, growing the plant cell [is cultured in planta] into a plant.

**Contact information**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Medina A. Ibrahim whose telephone number is (571) 272-0797. The Examiner can normally be reached Monday -Thursday from 8:00AM to 5:30PM and every other Friday from 9:00AM to 5:00 PM . Before and after final responses should be directed to fax nos. (703) 872-9306 and (703) 872-9307, respectively.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Amy Nelson, can be reached at (571) 272-0804.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

8/31/04

Mai

*Medina A. Ibrahim*

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MEDINA A. IBRAHIM  
PATENT EXAMINER